

## **<sup>68</sup>Ga-DOTATATE PET/CT on the Follow-up of Patients with Medullary Thyroid Carcinoma**

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### **Abstract**

*The purpose of this study is to evaluate the impact of <sup>68</sup>Ga-DOTATE PET/CT on the management of medullary thyroid carcinoma (MTC). Eighteen patients (9 males and 9 females) with MTC who underwent <sup>68</sup>Ga-DOTATE PET/CT for elevated calcitonin(Ct) levels were included in this study. Histopathological data, laboratory findings, <sup>68</sup>Ga-DOTATE PET/CT findings were evaluated for each patient. <sup>68</sup>Ga-DOTATE PET/CT imaging findings were negative in 5 of 18 patients (27.8%) and positive in 13 of 18 patients (72.2%). The mean Ct level of patients with positive findings was higher than others. <sup>68</sup>Ga-DOTATE PET/CT was insufficient for detecting liver metastases in two patients who exhibited hypermetabolic uptakes consistent with solitary metastases in the liver on <sup>18</sup>FDG-PET/CT. We believe that <sup>68</sup>Ga-DOTATE PET/CT plays an important role in the management of MTC patients with recurrent or metastatic disease. Its sensitivity is directly proportional to the levels of serum Ct. However, it may have limitations in detecting liver metastases.*

**Keywords:** MTC, <sup>68</sup>Ga-DOTATE, PET/CT, Ct

### **Introduction**

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine cancer. The origin of this tumor is thyroid parafollicular C-cells. It comprises approximately 1% to 2% of all thyroid cancers (1, 2). C-cells produce calcitonin hormone (Ct) which is directly related to the number of C-cells. Ct is an

important tumor marker for MTC patients following thyroidectomy (3).

It is not always easy to find the source of an increased Ct (4).

Various imaging techniques are used for this, especially conventional methods. However, morphological features are not always diagnostic.

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For this reason, metabolic and functional imaging techniques have found an area in this regard.

Fluorine-18 fluorodeoxyglucose (18FDG) and fluorine-18 dihydroxyphenylalanine (18F-DOPA) are fluorine-18-containing PET radiopharmaceuticals used in detecting MTC (5). <sup>68</sup>Ga tagged somatostatin analogs (<sup>68</sup>Ga-DOTATATE, <sup>68</sup>Ga-DOTATOC, <sup>68</sup>Ga-DOTANOC) are used for the diagnosis of neuroendocrine tumors. MTC also displays features of a tumor with neuroendocrine features. The purpose of this study is to evaluate the impact of <sup>68</sup>Ga-DOTATE PET/CT on the management of MTC.

### Method

Eighteen patients (9 males and 9 females) with MTC who underwent <sup>68</sup>Ga-DOTATE PET/CT for elevated Ct levels were included in this study. Mean age was 53.3±9.2. The chemiluminescence immunoassay method was used for measuring Serum Ct levels (normal range 0–5.8pg/mL)

<sup>68</sup>Ga was produced from a <sup>68</sup>Ge/<sup>68</sup>Ga radionuclide generator, combined with the DOTATE peptide in our laboratory. A dose of 2–3 MBq/kg of synthesized <sup>68</sup>Ga-DOTATATE was injected intravenously into the patients. Forty-five minutes after injection, PET/CT imaging was performed on the patients using a whole-body PET/CT device (Siemens Biograph 2 LSO).

Two nuclear medicine specialists evaluated the <sup>68</sup>Ga-DOTATE PET/CT images. Standard uptake values (SUV<sub>max</sub>) were calculated for each patient. Histopathological data, laboratory findings, <sup>68</sup>Ga-DOTATE PET/CT findings were evaluated for each patient. Findings of other imaging modalities (18FDG PET-CT, USG, CT, etc.) were also evaluated.

SPSS 18.0 statistical software program was used for the evaluation of data. Student's t-test, Mann-Whitney U-test, and Spearman's correlation analysis were the statistical tests used for the evaluation. P-values less than 0.05 were considered statistically significant.

### Results

#### Evaluation of <sup>68</sup>Ga-DOTATE PET/CT imaging findings:

<sup>68</sup>Ga-DOTATE PET/CT findings were negative in 5 out of 18 patients (27.8%). The mean Ct level of these patients was 513.4±565 pg/mL (min 128 - max 999) (Table 1).

**Table 1:** Calcitonin levels of patients according to <sup>68</sup>Ga-DOTATE PET/CT findings.

	Mean Ct levels (pg/mL)
<sup>68</sup> Ga-DOTATE PET/CT (+) with distant metastasis (n:6) (33.4%)	6281±7353 (min 86- max 14380)
<sup>68</sup> Ga-DOTATE PET/CT (+) without distant metastasis (n:7) (38.8%)	591±261 (min 93- max 634)
<sup>68</sup> Ga-DOTATE PET/CT (-) (n:5) (27.8%)	513.4±565 (min 128- max 999).

n, patient number; (+), positive finding; (-), negative finding; Ct, Calcitonin.

<sup>68</sup>Ga-DOTATE PET/CT imaging findings were positive in 13 out of 18 patients (72.2%). The mean Ct level of these patients was 3271.5±7481 pg/mL (min 86 - max 14380), which was higher than patients with negative <sup>68</sup>Ga-DOTATE PET/CT imaging findings. However, this difference was not statistically significant (p>0.05).

In 6 patients (33.4%) with positive findings on <sup>68</sup>Ga-DOTATE PET/CT scan, distant metastasis was observed. The mean Ct level of metastatic patients was 6281±7353 pg/mL (min 86 - max 14380).

Among these patients, three had both bone and lung metastases, while lymph nodes were observed in the head-neck and/or mediastinal regions. In the remaining 3 patients, distant involvement was limited to bone metastasis, with two of them having local recurrent disease involving head-neck and mediastinal lymph nodes.

Among the 7 patients (38.8%) who had positive findings on <sup>68</sup>Ga-DOTATATE PET/CT scan, there was local disease and lymph node involvement. The regions affected by lymph node involvement were head-neck and mediastinum. The mean Ct level of these patients was 591±261 pg/mL (min 93 - max 634), which was lower than patients with distant metastasis on <sup>68</sup>Ga-DOTATATE PET/CT. However, the difference was not statistically significant ( $p>0.05$ ). In 3 patients, lymph node metastases were confirmed histopathologically after neck dissection. In the remaining 4 patients, <sup>68</sup>Ga-DOTATATE PET/CT scan findings were consistent with other imaging modalities (USG, CT...) and calcitonin levels. Thus, it was concluded that they were pathological lymph node abnormalities.

### Discussion

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine cancer that can occur sporadically (75%) or in a familial pattern (25%) (6). It is known to be more aggressive than differentiated thyroid cancer (DTC), and metastases are not uncommon. At initial diagnosis, localized disease is present in only 48% of the patients (7). Common sites of metastatic disease include cervical and mediastinal lymph nodes (35% of patients at initial diagnosis), as well as the bone, lung, and liver (8). Distant metastases occur in approximately 20% of MTC patients (9). In our study, we detected distant metastasis in 33.3% of patients using

<sup>68</sup>Ga-DOTATATE PET/CT. The main treatment for MTC is surgery (1).

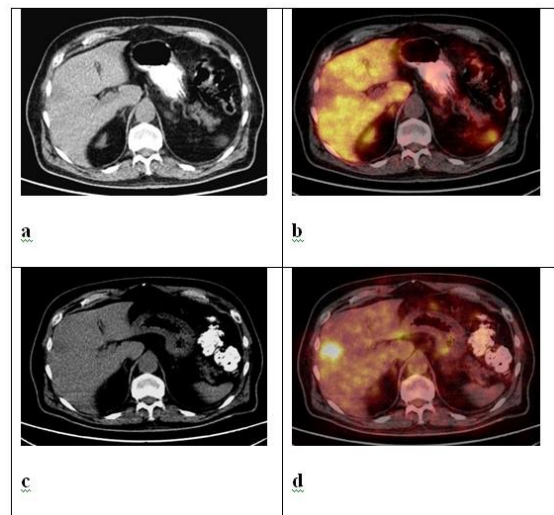
The most valuable tumor marker in MTC follow-up is serum Calcitonin (Ct) level. Carcinoembryonic antigen (CEA) is another frequently used marker, but it has low sensitivity and specificity compared to Ct (10, 11, 12). After successful surgery, Ct levels are usually below 10 pg/mL in the postoperative 8-10 weeks. However, up to half of the cases experience disease recurrence despite curative surgery (3). Rising Ct levels during follow-up indicate residual, recurrent, or metastatic disease (6). Early detection of residual/recurrent tumors is crucial for prognosis and disease management (13, 14).

Detecting recurrent and metastatic foci in MTC can be challenging due to the lack of completely efficient diagnostic tools. Factors such as small lesion size and postoperative scar tissue can make the detection of MTC lesions difficult (15). Various morphological and functional imaging methods can be used for this purpose. Neck ultrasound (USG) may be sufficient when Ct levels are under 150 pg/mL (3). However, when Ct levels are higher, multiple imaging tests (MRI, CT, bone scintigraphy, PET-CT, etc.) may be employed. Despite these efforts, persistent MTC cannot be detected in about half of the patients (16). The sensitivity of these tests ranges between 50% and 80% (1). In our study, the sensitivity of <sup>68</sup>Ga-DOTATATE PET/CT was 72.2%.

PET scan has a controversial role in the detection of MTC. The initial recommended PET radiopharmaceutical for MTC is <sup>18</sup>F-DOPA, which exhibits higher sensitivity, especially in patients with serum Ct >500 pg/mL (17). However, obtaining this agent can be challenging in many centers.

Another frequently used PET radiopharmaceutical is  $^{18}\text{F}$ FDG. Unfortunately, MTC can show lower sensitivity to FDG, similar to other neuroendocrine tumors. However, tumor differentiation and dedifferentiation can increase FDG uptake (15). The reported sensitivity of FDG PET ranges from 41% to 78% in various studies for MTC patients (16, 18, 19). The sensitivity increases particularly with higher Ct levels, especially when Ct levels exceed 1,000 pg/mL (16). PET/CT with  $^{68}\text{Ga}$ -labeled somatostatin-analog peptides, including  $^{68}\text{Ga}$ -DOTATATE,  $^{68}\text{Ga}$ -DOTATOC, and  $^{68}\text{Ga}$ -DOTANOC, is routinely used in neuroendocrine tumor imaging (21). These tracers have a high affinity for the type 2 somatostatin receptor (SSTR2), which MTC cells express due to their neuroendocrine origins. The sensitivity of  $^{68}\text{Ga}$ -DOTATATE PET/CT in imaging MTC patients varies widely in the literature, ranging from 33.3% to 75.6% (12, 21-23). In our study, we found this ratio to be 72.2%. This variability can be explained by the fact that MTC expresses SSTRs in lower amounts compared to other neuroendocrine tumors, resulting in more variability (24). The sensitivity is directly proportional to the Ct levels, as demonstrated in a study by Tuncel et al., where patients with Ct levels below 60 pg/mL did not show positive findings on PET/CT (25). On the other hand, when Ct levels exceed 500 pg/mL, the performance of  $^{68}\text{Ga}$ -DOTATATE PET/CT is optimal (26). Our findings align with the literature, as patients with positive findings on  $^{68}\text{Ga}$ -DOTATATE PET/CT had higher Ct levels compared to others. However, this difference was not statistically significant ( $p > 0.05$ ), which may be attributed to the small number of patients in our study.

Several studies in the literature have compared  $^{18}\text{F}$ FDG PET/CT and  $^{68}\text{Ga}$ -DOTATATE PET/CT for MTC (5, 21-23, 27). The overall consensus tends to favor  $^{68}\text{Ga}$ -DOTATATE PET/CT over  $^{18}\text{F}$ FDG PET/CT (28). In particular,  $^{68}\text{Ga}$ -DOTATATE PET/CT has shown superiority in detecting bone and lymph node metastases compared to  $^{18}\text{F}$ FDG PET/CT (23). However,  $^{68}\text{Ga}$ -DOTATATE PET/CT may be prone to missing liver metastasis. The physiological uptake of  $^{68}\text{Ga}$ -DOTATATE in the liver is significantly high, which can lead to a low lesion-to-background ratio. As a result, liver metastases, particularly those with a small size, may be overlooked (12). In our study, we discovered that  $^{68}\text{Ga}$ -DOTATATE PET/CT was insufficient for detecting liver metastases in two patients who exhibited hypermetabolic uptakes consistent with solitary metastases in the liver on  $^{18}\text{F}$ FDG-PET/CT (figure 1).



**Figure 1:** Fifty-eight years old male patient. Ct level was 192 pg/mL.  $^{68}\text{Ga}$ -DOTATATE PET/CT [transaxial CT (a), transaxial PET/CT fusion (b)] and  $^{18}\text{F}$ FDG PET/CT [transaxial CT (c), transaxial PET/CT fusion (d)] images of the patient. Focal hypermetabolic uptake compatible with metastasis in the liver were detected with  $^{18}\text{F}$ FDG PET/CT, while no pathological uptake was found with  $^{68}\text{Ga}$ -DOTATATE PET/CT.

## Conclusions

In conclusion, we believe that <sup>68</sup>Ga-DOTATATE PET/CT plays an important role in the management of MTC patients with recurrent or metastatic disease. Its sensitivity is directly proportional to the levels of serum Calcitonin (Ct). The detection rate of lesions increases with higher Ct levels, particularly above 1000 pg/mL. However, it may have limitations in detecting liver metastases. If there is any suspicion of liver metastases, additional imaging methods may be necessary to ensure comprehensive evaluation and accurate detection.

## Conflict of Interests

The authors declare that no conflict of interest exists.

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